

▪ **Copper Catalysed Conjugate Addition**

Conjugate Addition Routes to 2-alkyl-2,3-dihydroquinolin-4(1*H*)-ones and 2-alkyl-4-hydroxy-1,2-dihydroquinoline-3-carboxylates

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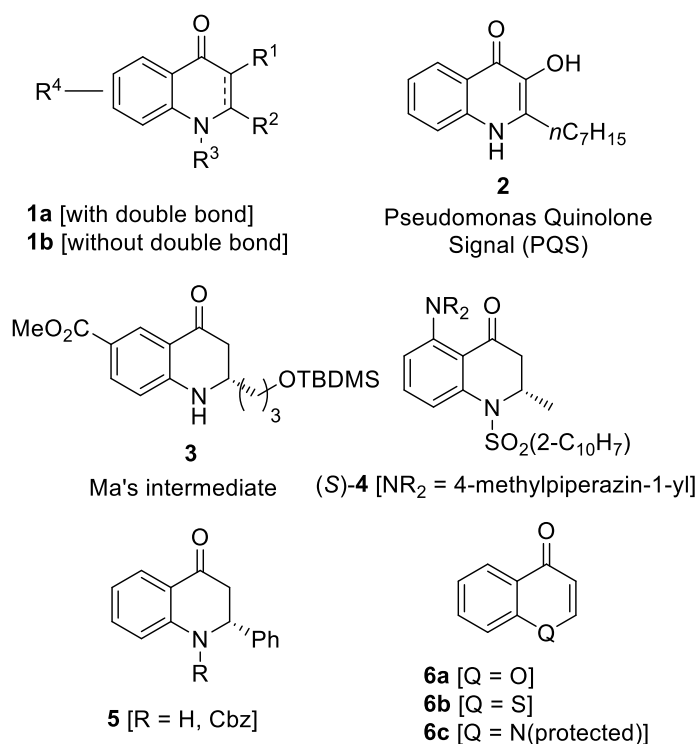
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Abstract: Under CuBr·SMe₂/PPh₃ catalysis (5/10 mol-%) RMgCl (R = Me, Et, *n*Pr, CH=CH₂, *n*Bu, *i*Bu, *n*C₅H₁₁, *c*C₆H₁₁, Bn, CH₂Bn, *n*C₁₁H₂₃) readily (-78 °C) undergo 1,4-addition to Cbz or Boc protected quinolin-4(1*H*)-ones to provide 2-alkyl-2,3-dihydroquinolin-4(1*H*)-ones (14 examples, 54-99% yield). Asymmetric versions require AlEt₃ to Boc-protected ethyl 6-substituted 4(1*H*)-quinolone-3-carboxylates (6-R group = all halogens, *n*/*i*/*t*-alkyls, CF₃) and provide 61-91% yield, 30-86% *ee*; any halogen, Me, or CF₃ provide the highest stereoselectivities (76-86% *ee*). Additions of AlMe₃ or Al(*n*C₈H₁₇)₃ provide ~45 and ~75% *ee* on addition to the parent (6-R = H). Ligand (*S*)-(BINOL)P-N(CHPh₂)(*c*C₆H₁₁) provides the highest *ee* values engendering addition to the *Si* face of the 4(1*H*)-quinolone-3-carboxylate. Allylation and deprotection of a representative 1,4-addition product example confirm the facial selectivity (X-ray).

Introduction

Quinolone sub-structure cores **1a** and their dihydro-analogues **1b** (Scheme 1) constitute privileged starting materials in medicinal and natural product chemistry. The former core has been a lynchpin in antibiotic development for more than 50 years,^[1] most recently in quorum sensing approaches, e.g. the moderation of bacterial activity engendered by species such as **2**.^[2] The latter core **1b** has been deployed in the syntheses of a range of natural and biologically active molecules, for example Ma's intermediate (**3**)^[3], used in the synthesis of martinellid acid (a natural Bradykinin antagonist); and in the related **4**; active at 7 nM towards 5-HT₆ serotonin receptors.^[4] Compounds **3-4** are exemplary of the recent move to explore sp³ rich heterocycles in medicinal chemistry.^[5] Such concepts are poorly explored for dihydroquinolones, with **5** being the only common 'model compound' encountered, providing significant stereoselectivities for *aryl* additions and being attained by either Rh-^[6] or Pd-catalysed^[7] ArM (M = ZnCl, BAR₃), addition providing **6c** (R = *aryl*) in 40-99+% *ee*, or by a variety of organocatalytic closures (0-99+% *ee*) leading to the same core but from different 2-

aminochalcone and related intermediates.^[8] As both these approaches do not presently allow access to more biologically more interesting sp^3 substituents (e.g. **3-4** etc.) we sought to study presently less explored *alkyl* organometallic additions to **6c**. This seemed potentially profitable as catalytic enantioselective 1,4 alkyl additions to related **6a-b** (Y = O, S with R = alkyl) are already known (9-96% ee).^[9]



Scheme 1. Quinolone and derived dihydro-analogues of relevance to this publication.

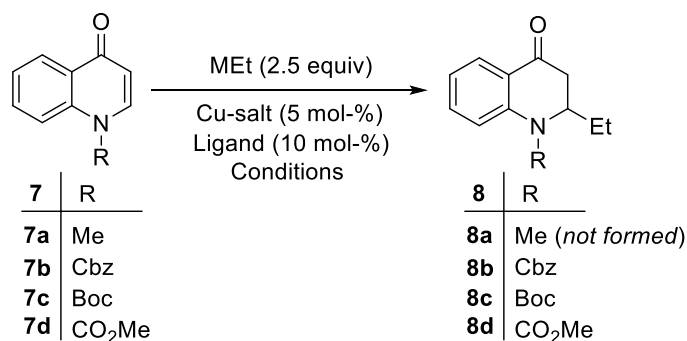
Results and Discussion

Additions to protected quinolin-4(1H)-ones (**7**)

The protected acceptors **7a-d** (within Table 1) are readily accessible from commercial quinolin-4(1H)-one, which is itself also available from 2-nitroacetophenone via standard heterocyclic chemistry.^[10] As stoichiometric copper reagents had already been used in copper-promoted additions to **7a** (for aza analogues of the natural product Wrightiadione.^[11]), we tested this substrate under catalytic conditions, but it proved too deactivated to react. The more electron deficient **7b** still performed poorly with $ZnEt_2$ or $AlEt_3$, under typical conjugate addition conditions. Runs 1-2 were the best outcomes we could attain from a range of conditions. As we could readily confirm that the stoichiometric cuprate $MgBr[CuEt_2]$ readily added to **7b** in THF upon reaction at -78 to -20 °C affording a 65% isolated yield of **8b** we trialed catalytic versions of this chemistry. In the absence of added ligands conversions were modest in THF (Run 3), and worse upon addition of Et_2O (Run 4) due to the insolubility of **7b** in this solvent. Remarkably, although **7b** is also insoluble in 2-MeTHF at low temperature, this solvent produced a very rapid 1,4-addition (within 5 mins), which could be somewhat further promoted by simple phosphorus ligand addition (Runs 5-7). Simply increasing the overall reaction time to 1 h led to complete conversion in both the Cbz and Boc protected quinolin-4(1H)-ones (**7b-c**) (Runs 8-9) while the methyl carbamate (**7d**) was inferior (Run 10). By employing these optimal conditions of Table 1 we could show the synthetic scope of the 2-MeTHF reaction conditions (Scheme 2); which contains compounds of clear synthetic and biological utility. Species **8b-c** and **9** have only been mentioned passingly in alternative methodology aimed at biologically active targets,^[12] while all other isolated examples in Scheme 2 are novel. Certain limitations were noted in the chemistry of Scheme 2: (i) the

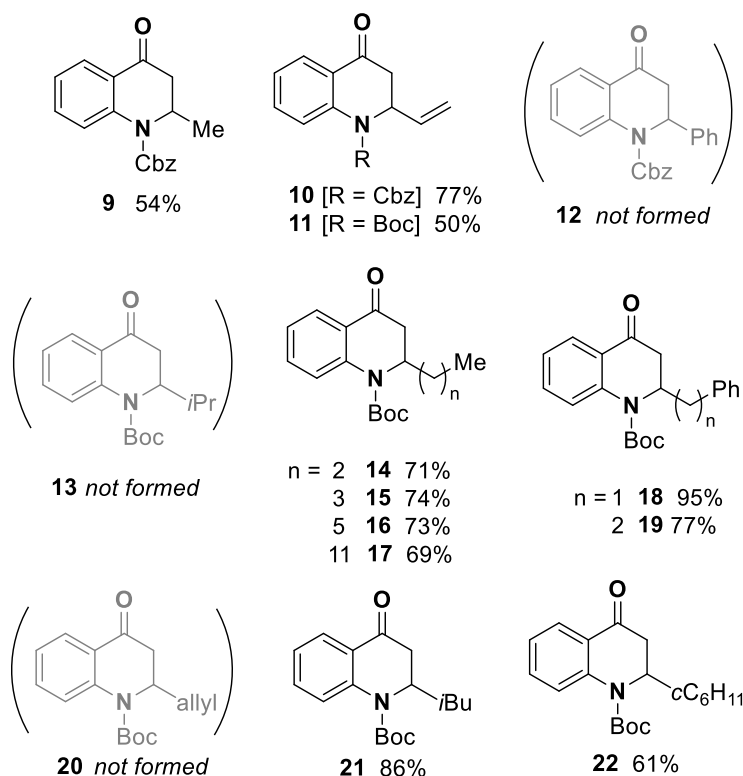
lowest yields were associated with addition of MeMgX to **7b** while **7c** did not participate in the same reaction; (ii) the catalytic reaction is sensitive to α -branching in the Grignard (e.g. *i*PrMgBr and PhMgBr do not react and *c*C₆H₁₁MgBr give a reduced yield; (iii) Allyl Grignard did not participate in the reaction.

Table 1. Optimisation of EtMgBr addition to *N*-protected quinolin-4(1*H*)-ones **7**.



Run	7	MEt	Cu-source	Ligand	Solvent	Temp (°C)	Time	Conv. (%) ^[a]
1	7b	ZnEt ₂	Cu(OAc) ₂	P(OPh) ₃	THF	-10	12 h	–
2	7b	AlEt ₃	Cu(OTf) ₂	P(OPh) ₃	THF	-10	18 h	<25
3	7b	EtMgBr	CuBr·SMe ₂	–	THF	-50 to -10	1.5 h	34
4	7b	EtMgBr	CuBr·SMe ₂	–	THF/Et ₂ O (1:1)	-78 to -20	1 h	31
5	7b	EtMgBr	CuBr·SMe ₂	–	2-MeTHF	-78	5 min	75
6	7b	EtMgBr	CuBr·SMe ₂	P(OPh) ₃	2-MeTHF	-78	5 min	88
7	7b	EtMgBr	CuBr·SMe ₂	PPh ₃	2-MeTHF	-78	5 min	96
8	7b	EtMgBr	CuBr·SMe ₂	PPh ₃	2-MeTHF	-78	1 h	>99 ^[b]
9	7c	EtMgBr	CuBr·SMe ₂	PPh ₃	2-MeTHF	-78	1 h	>99 ^[c]
10	7d	EtMgBr	CuBr·SMe ₂	PPh ₃	2-MeTHF	-78	1 h	78

[a] Determined by ¹H NMR on the crude reaction mixture. [b] Isolated yield 80%. [c] Isolated yield 99%.

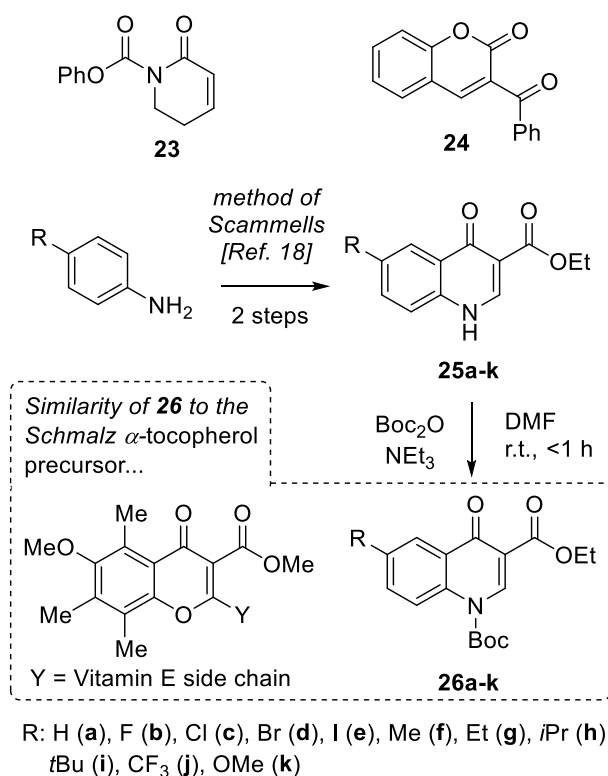


Scheme 2. Scope and limitations of $\text{CuBr}\cdot\text{SMe}_2/\text{PPh}_3$ catalysed 1,4 Grignard addition to acceptors **7**. Isolated yields.

Having established viable catalysis we turned our attention to the potential for an asymmetric version. Using the conditions of Scheme 2 but truncating the reaction time to just 2.5 minutes for the EtMgBr 1,4-addition to **7b** is instructive. In the absence of any added ligand $\text{CuBr}\cdot\text{SMe}_2$ (5 mol-%) a 35% conversion to **8b** is already realised. In the presence the same copper loading and conditions, but with added phosphine ligands (10 mol-%) improved conversions are realised: P(OPh)_3 (88%), PPh_3 (73%) and $\text{P}(\text{cC}_6\text{H}_{11})_3$ (92%). This indicates that any ligand accelerated catalysis^[13] is modest and not strongly affected by the σ/π -donor characteristics of the phosphine. In line with these observations screening of a small diverse library of chiral ligands (exemplars **LA-LF**)^[10] produced at best 1-11% ee at conversions of 21-76%. The low levels of asymmetric induction realised are likely due to diverse substrate coordination shown by Mg(II) in 2-MeTHF.^[14]

Additions to Boc-protected ethyl 6-substituted 4(1H)-quinolone-3-carboxylates (**26**)

One way to overcome the issues raised by substrates **7** is to add additional coordinative groups to the acceptor to provide both greater control of the asymmetric transition state conformation and increase its reactivity allowing the use of more selective (more covalent) organometallics (ZnR_2 , AlR_3). Substrates **23**^[15]-**24**^[16] (Scheme 3) represent examples of such approaches. We therefore initiated study of acceptors **26** which are attractive due to their similarity to Schmalz's asymmetric synthesis of Vitamin E (94% ee for 1,4 AlMe_3 addition);^[17] and as Scammells has described very short preparation of the parent precursor **25a**.



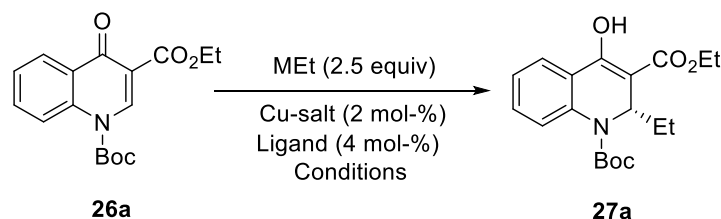
Scheme 3. Preferred heterocyclic motifs for improved selectivity in asymmetric additions and the synthesis of preferred acceptor **26**.

Synthesis of the acceptor library **26a-k** proceeded as expected,^[10] but two points are worth noting: (i) the use of Eaton's reagent to cyclise the 6-substituted 4-oxo-1,4-dihydroquinolines **25** is much preferred over traditional phosphoric acids or high temperature cyclisations in Ph_2O and we found this can be telescoped into a one-pot procedure; (ii) in Boc protection of **25**,

washing with $\text{LiCl}_{(\text{aq})}$ to remove DMF avoids the degradation that even mildly acidic washes would cause.

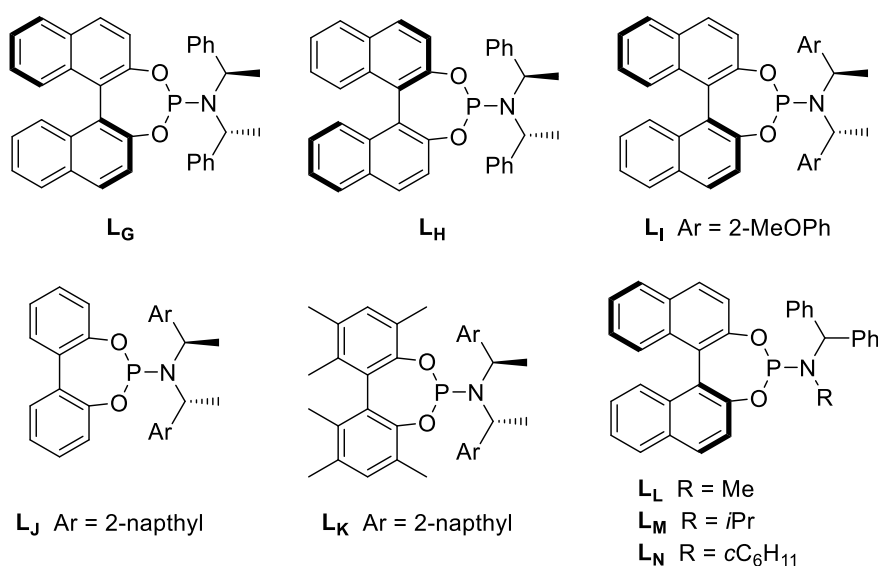
Preliminary investigations focused of asymmetric catalytic studies on **26a** (Table 2). Previous studies had already revealed the ethyl ester is preferred over both smaller and larger groups (Me, CHPh_2) are inferior and that phosphoramidites are the optimal ligand class. The ligand structures used in the final optimisation are shown in Scheme 4.

Table 2. Optimisation of AlEt_3 addition to Boc-protected 4(1*H*)-quinolone-3-carboxylate **26a**.



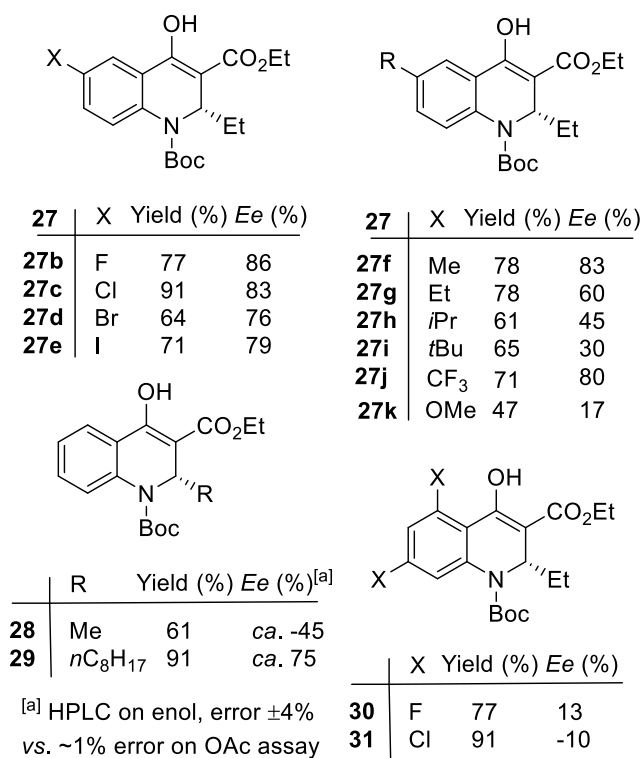
Run	MEt	Cu-source	Ligand	Solvent	Temp (°C)	Time (h)	Conv. (%) ^[a]	Ee (27a)
1	AlEt_3	$\text{Cu}(\text{OTf})_2$	L_G	CH_2Cl_2	-10	<0.1	>99	<1
2	AlEt_3	$\text{Cu}(\text{OTf})_2$	L_G	THF	-10	0.5	>99	-18
3	AlEt_3	$\text{Cu}(\text{OTf})_2$	L_G	Et_2O	-10	1	>99	40
4	AlEt_3	$\text{Cu}(\text{OTf})_2$	L_G	Et_2O	-25	1	>99	60
5	AlEt_3	$\text{Cu}(\text{OAc})_2$	L_G	Et_2O	-25	3	96	52
6	AlEt_3	$\text{Cu}(\text{MeCN})_4\text{BF}_4$	L_G	Et_2O	-25	3	98	45
7	ZnEt_2	$\text{Cu}(\text{OTf})_2$	L_G	Et_2O	-25	<0.1	>99	15
8	AlEt_3	$\text{Cu}(\text{OTf})_2$	L_G	Et_2O	-40	6	98-99	65
9	AlEt_3	$\text{Cu}(\text{OTf})_2$	L_G	Et_2O	-40	6-24	>99 ^[b]	65
10	AlEt_3	$\text{Cu}(\text{OTf})_2$	L_H	Et_2O	-40	24	22	-
11	AlEt_3	$\text{Cu}(\text{OTf})_2$	L_I	Et_2O	-40	24	87	5
12	AlEt_3	$\text{Cu}(\text{OTf})_2$	L_J	Et_2O	-40	24	>99	12
13	AlEt_3	$\text{Cu}(\text{OTf})_2$	L_K	Et_2O	-40	24	>99	26
14	AlEt_3	$\text{Cu}(\text{OTf})_2$	L_L	Et_2O	-40	24	>99	2
15	AlEt_3	$\text{Cu}(\text{OTf})_2$	L_M	Et_2O	-40	24	>99	70
16	AlEt_3	$\text{Cu}(\text{OTf})_2$	L_N	Et_2O	-40	24	>99 ^[c]	77^[d]

^[a] Determined by ^1H NMR on the crude reaction mixture. ^[b] Isolated yield 68%. ^[c] Isolated yield 73%. ^[d] 77-82% ee at 4 mol-% $\text{Cu}(\text{OTf})_2$ and 8 mol-% **L_N**.



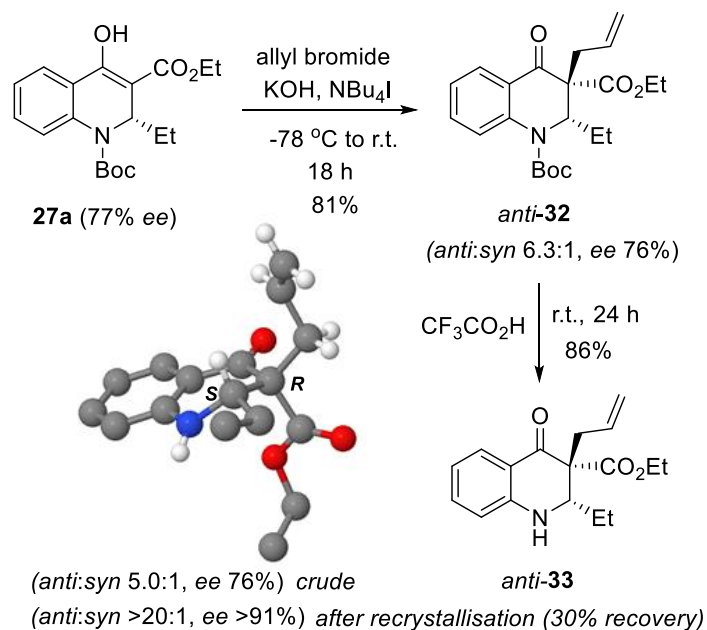
Scheme 4. Ligands used for catalytic asymmetric additions of MR to acceptor **26a**.

Initial trials (Table 2) identified Et₂O as an optimal solvent (Runs 1-3) and that copper(II) triflate was the optimal pre-catalyst for asymmetric AlEt₃ 1,4-addition (Runs 4-6) using (*S,R,R*) Feringa's ligand **L₆** as a starting phosphoramidite. Alternative additions of ZnEt₂ provided poorer performance (Run 7 is representative). For AlEt₃ additions cooling the reaction to -40 °C led to the highest ee value, but an increase in reaction time is required (Runs 8-9). We postulate that the success of the ether solvent is due to the relative insolubility of **26a** in it at low temperature which somewhat moderates background (uncatalysed) reactions. At -40 °C in the absence of any catalyst a 74% conversion of **25a** is seen at 24 h. Lower temperatures could not be used to further moderate this, as all reactions (catalysed or background) shut down at -50 °C. We have seen similar effects before.^[16] Ligand modification to include addition coordination (**L₁**, Run 11), increase in steric bulk of both the amine (**L₂**) or atropisomeric diol (**L₃**) (Runs 12-13) had detrimental effects on the selectivity. The performance of the dissymmetric ligands (**L₄-L₆**) was maximised for a cyclohexyl substituent (Runs 14-16). Finally, as the reaction is close to viability at -40 °C we assured its reproducibility, performance and conversion by increasing the catalyst loadings to 4 mol-% Cu(OTf)₂ and 8 mol-% **L₆**. Using these optimised conditions we investigated the effect of the 6-substituent on the catalytic reaction performance (Scheme 5).



Scheme 5. Scope and limitations of substitution patterns for 4(*1H*)-quinolone-3-carboxylate acceptors.

The behaviour of **27a-k** indicate that electron withdrawing groups in the 6-position increase the stereoselectivity of AlEt₃ 1,4-addition. Steric demand in the 6-position has a detrimental effect on the selective transition state, but less so than electron factors. With respect to the alane, AlMe₃ reversed the sense of asymmetric induction (**28**), but longer linear alkyl chains were tolerated and behaved similarly to AlEt₃ (**29**). Disubstituted **30-31** are clearly not accepted by the reaction transition state, but the root cause of this issue is not apparent at present. Due to the apparent reversals of enantioselectivity (e.g. **27a** vs. **28**), based on sign of optical rotation and HPLC enantiomer elution order, it became important to identify the absolute sense of the asymmetric induction engendered by (*S*)-**L₆** in AlEt₃ addition to **26a**, and by implication other combinations of acceptors and alanes. Unfortunately, all of the direct conjugate addition products **27** we encountered were oils. However, we could overcome this issue and attain a crystalline derivative by manipulation of **27a** (Scheme 6).



Scheme 6. Stereo-correlation of (+)-**27a** to crystallographically characterised (2*S*,3*R*)-**33** via selective allylation, to *anti*-**32**, and Boc-deprotection. Only hydrogens on the allyl, amine and C2-methine groups of **33** are shown. Selected bond distances: N1-C2 1.450(6), 1.439(6); C2-C3 1.555(6), 1.558(6); C3-C4 1.524(7), 1.543(7) Å and N1-C1-C2-C3 torsion angle: 43.4(5), 48.2(5)°. There are two independent molecules in the unit cell of **33**.

A sample of 77% ee (+)-**27a** was allylated under non-polar mild conditions leading to the formation of a major allyl *anti* diastereomer **32** with the same optical purity, within experimental error as the starting material. Deprotection of **32** with trifluoroacetic acid leads to formation of a similar mixture of stereoisomers, of which the *anti*-(**33**) species is significantly the most abundant. Fortunately, slow addition of pentane to concentrated ether solutions of the **33** mixture leads to the formation of modest crops of yellow needles of (+)-**33**, which by crystallography are the single isomer *anti*-(+)-(2*S*,3*R*)-**33**.^[10] Thus (+)-**27a** also has the 2*S* configuration presented throughout this paper. Based on the similarity of their chiral (Chiralpak AD-H) HPLC enantiomer elution and the homology of their polarimetry results we tentatively suggest that **27a-k** and **28-31** have the stereochemistry implied herein.

Conclusions

While new 1,4-addition of *alkyl* Grignard reagents to protected quinolin-4(1*H*)-ones (**7**) proceed efficiently (54-99% yield) under CuBr·SMe₂/PPh₃ catalysis (5/10 mol-%) attempts to render the process asymmetric are not successful (*ee*_{max} ~11%). However, modification of the quinolin-4(1*H*)-one core by addition of an ester directing/activating group at the 3-position allows asymmetric additions of AlR₃ (R = Me, Et, *n*C₈H₁₇) under Cu(OTf)₂/phosphoramidite (4/8 mol-%) catalysis. The best ligands are the dis-symmetric ligands introduced by Fletcher, especially (*S*)-**L_N**.^[19] Stereoselectivities in the range from: -45 to +86% ee are observed, with the highest selectivities being associated with those 4(1*H*)-quinolone-3-carboxylate acceptors (**26**) bearing small electron withdrawing substituents at the 6-position. The sense of asymmetric induction, due to (*S*)-**L_N**, could be determined by C3-allylation and subsequent *N*-deprotection to afford crystals of ethyl (2*S*,3*R*)-3-allyl-2-ethyl-2,3-dihydro-4(1*H*)-quinolone-3-carboxylate (2*S*,3*R*)-(**33**). As no general ligand providing >90% ee over a range of 4(1*H*)-quinolone-3-carboxylates was identified it is likely that individual substrate optimisation will be required. Rather than *ad hoc* screening we propose *in silico* ligand screening of a test transition state, modelled out of our own mechanistic studies,^[S20] but

using the substrates employed here may be an attractive alternative strategy to the discovery of such systems. Such investigations are our next target.

Experimental Section

Details of our general laboratory set-up and instrumentation have been already published.^[21] Procedures and data for the processes and compounds described in this paper are within the Supporting Information.

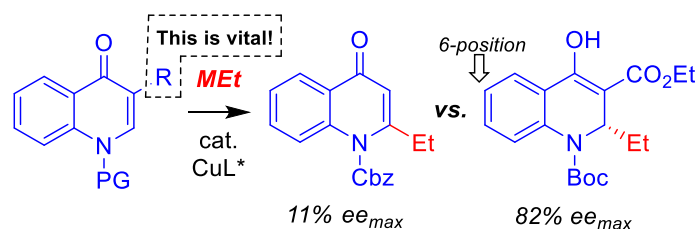
Acknowledgements

AK thanks Key Organics Ltd, the Engineering and Physical Sciences Research Council (EPSRC CASE Award 1507028) and the University of Nottingham for financial support. SW is very grateful to Dr David Robinson (Nottingham Trent University, UK) for discussions on stereochemistry and to Profs H.-G. Schmalz (University of Cologne, Germany) and Alex Alexakis (University of Geneva, Switzerland) for providing small initial samples of some of the ligands used in this study.

Keywords

• Alanes • Copper • Asymmetric Catalysis • Michael addition • Phosphane ligands

Graphical Abstract



Graphical Abstract Text:

Directing ester functions (R = CO₂Et) 'give a big hand' to copper catalysed 1,4-additions of organometallics. Synthetically useful 6-halo building blocks are accessed.

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